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Three Year Follow-Up of Acromegalic Patients Treated with Intramuscular Slow-Release Lanreotide*

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ABSTRACT

Somatostatin analogs are an alternative treatment to pituitary surgery and radiotherapy in acromegalic patients. Recently, a depot long-lasting formulation of slow release (SR) lanreotide has been shown to be effective in the short-term control of GH hypersecretion in acromegalic patients. We report the long-term follow-up of a cohort of 22 acromegalic patients treated with SR lanreotide during 1–3 yr. Thirteen females and 9 males, age 51 ± 3 yr, presented with macroadenomas (n = 12), microadenomas (n = 8), or empty sella (n = 2). Seven patients previously had undergone a partial surgical removal of their adenomas, and 21 of them had mean plasma GH levels less than 5 μg/L during a previous octreotide treatment. According to GH values recorded after 3 months of twice monthly 30 mg SR lanreotide im injection, SR lanreotide was administered every 14 days (n = 13) or every 10 days (n = 9). At the 6-month visit, mean GH values were 5 μg/L or less in 68% and 2.5 μg/L or less in 27% of patients, and these results remained unchanged during the 1–3 yr follow-up period. During SR lanreotide treatment, the mean insulin-like growth factor I (IGF-I) concentrations remained in the normal range in 63% of patients. No escape from the treatment occured in any of the cases. A significant decrease of the pituitary tumor volume was observed in 3 (13%) patients. The main side effect consisted of minor digestive problems during 48 h after each injection and was reported by 13 patients. Biannual gallbladder echographies revealed the occurence of gallstones in 4 (18%) patients. In conclusion, these data confirm the efficacy and the tolerance of the long-term SR lanreotide administration (30 mg im every 10–14 days) in the control of acromegaly. (*J Clin Endocrinol Metab* **82:** 18–22, 1997)

SOMATOSTATIN analogs are an alternative treatment to pituitary surgery and radiotherapy in acromegalic patients (1–3). Normalization of plasma growth hormone (GH) and/or insulin-like growth factor (IGF-I) levels have been achieved in acromegalic patients treated for long term with the somatostatin analog octreotide. Recently, it has been shown that im injections of 30 mg of a new cyclic octapeptide analog of somatostatin, slow-release (SR) lanreotide (Somatuline, Ipsen Biotech Lab, Paris, France) suppressed for 10–14 days the GH hypersecretion of acromegalic patients (4, 5). In short-term studies, SR lanreotide achieved a control of GH hypersecretion similar to that previously obtained with sc injections (6, 7) or with continuous infusion (8) of octreotide. To address the concerns of long-term efficacy and safety of SR lanreotide, 22 acromegalic patients have been enrolled in this unblunted, open study. Because of the variable suppressive effect of somatostatin analogs on GH hypersecretion previously reported (3), we only selected those patients considered to be responsive to the somatostatin analog octreotide, as their plasma GH level decreased to less than 5 μg/L during octreotide treatment or after a 100 μg sc octreotide test. The present report describes the results of the first 1–3 yr follow-up. The data obtained indicate that the SR lanreotide is safe and retains effectiveness in suppressing GH and IGF-I levels in acromegalic patients.

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Subjects and Methods

Patients

The 22 acromegalic patients included in this study were 13 women and 9 men, age 51 ± 3 yr (mean ± SEM). Nineteen presented with pure GH-secreting tumors and three with GH-PRL-secreting adenomas. On computed tomography (CT) scan or nuclear magnetic resonance imaging (MRI), 12 of these patients had a macroadenoma with suprasellar extension, 8 had an intrasellar microadenoma or a postoperative intrasellar tumor residue, and 2 had an empty sella. Seven patients had been treated by transphenoidal incomplete surgical resection of the pituitary tumor, performed at least 1 yr before this study. None of the patients had been treated by external radiation. For patients (n = 4, 7, 15) with GH-PRL-secreting adenomas, dopamine agonists (bromocriptine, CV 205–502) were associated with somatostatin analog therapy, but the dose was not changed during the 3-yr study. Twenty-one patients included in this study had been treated with sc injections (n = 13) or continuous infusion (n = 8) of octreotide (mean dose 385 ± 40 μg/day) for 16 ± 4 months. Treatment for diabetes mellitus (n = 4) and levothyroxine therapy (n = 5) for hypothyroidism or after thyroid surgery were continued without change. The individual characteristics of each patient are summarized in Table 1.

Study protocol

The present study was approved by the institutionnal ethics committee of the University of Aix-Marseilles (France). The diagnosis of acromegaly was based on clinical examination, elevated fasting serum GH levels that did not decrease to less than 5 μg/L in response to an oral (75 gr) or iv (1, 5 gr/kg) glucose load and elevated fasting serum IGF-I levels. We selected acromegalic patients considered to be responsive to the somatostatin analog octreotide, as their plasma GH level decreased to less than 5 μg/L during octreotide treatment (n = 21) or after a 100 μg sc octreotide test in a patient who was not initially treated with octreotide. Blood for all measurements of GH concentrations was withdrawn every hour for 8 h (between 0800–1500 h), before somatostatin analog treatment, after 6 months of octreotide treatment, on day 7 after octreotide withdrawal, after 3 months of SR lanreotide treatment, and subsequently every 6 months during long-term SR lanreotide treatment.

During the sampling period, patients were confined to bed and allowed to take a breakfast and a lunch. Plasma IGF-I levels were determined during octreotide treatment and before, at 3 months, and every 6 months during SR lanreotide therapy. During SR lanreotide treatment, serum GH and IGF-I concentrations were evaluated just before the next im injection of the somatostatin analog. Based on previous pharmacological studies (9, 10), all patients received sequentially an im injection of 30 mg SR lanreotide every 14 days up to the 3-month visit. Then, the treatment was maintained in 13 patients, or when hormonal evaluation was abnormal (mean plasma GH values greater than 5 μg/L) at the 3-month visit, SR lanreotide therapy was increased to one 30 mg im injection every 10 days in the 9 other patients.

Computed tomography scan or magnetic resonance imaging were performed before SR lanreotide treatment and then every 6 months. The largest diameter of the tumor was measured on coronal and axial sections: a significant shrinkage of the tumor was arbitrarily defined when such a diameter was reduced by 25% or more.

Serum TSH, free T_4, and glycosylated hemoglobin concentrations were measured before SR lanreotide therapy and were repeated every 6 months. A gallbladder echography was performed before enrollment in the study and then every 6 months during the protocol.

Hormone assays

Plasma GH concentration was measured using a double monoclonal antibody method (Elisa hGH, Cis-Bio-International, Gif-sur-Yvette, France). The detection limit of the assay was 0.5 μg/L. The intra- and interassay coefficients of variation were less than 2.8% and 4.4%, respectively. We considered that control of GH hypersecretion was obtained when the mean of 8 hourly GH values was less than 5 μg/L during somatostatin analog treatment. After an ethanol-acid extraction, the plasma IGF-I assay was performed by means of the IGF-I RIA kit from Nichols Institute Diagnostics (San Juan Capistrano, CA). The detection limit of the assay was 30 ng/mL. The intra- and interassay coefficients of variation were less than 5.2% and 11.2%, respectively. Normalization of IGF-I levels was considered to have been reached when they were under or equal to 300 ng/mL. Glycosylated hemoglobin levels were measured by high performance liquid chromatography (Diamat, Bio-Rad, Richmond, CA). The measurements of TSH and free T_4 were performed using commercial kits.

Data analysis

The results, presented as the mean ± SEM were compared with paired Student's t test before and during SR lanreotide treatment. A value of $P < 0.05$ was considered as significant in all tests.

Results

Twenty-two patients entered this long-term study. During octreotide treatment, patients had marked clinical improvement with decreased headaches (81%), paresthesia (73%), and soft tissue swelling (61%). During the wash-out period, very few symptoms (headaches) of acromegaly resumed. At the time of writing this report, patients have been evaluated after 6 (n = 22), 12 (n = 22), 24 (n = 17), and 36 (n = 13) months of SR lanreotide treatment. During SR lanreotide treatment, the control of clinical symptoms of acromegaly in each patient was similar to that previously achieved during octreotide treatment.

Effects of SR lanreotide on GH concentrations

In this cohort of 22 acromegalic patients, the mean plasma GH value at diagnosis was 26.8 ± 4.8 μg/L, and it fell to 2.3 ± 0.3 μg/L during octreotide treatment (Table 2). After the wash-out period, baseline plasma GH concentrations were 12.3 ± 3.4 μg/L. After a 3-month period of twice monthly 30 mg im injections of SR lanreotide, the mean baseline GH value recorded on day 14 after the last injection was 4.9 ± 0.6 μg/L ($P < 0.03$). Among the 22 patients, 13 had control of GH hypersecretion (3.1 ± 0.4 μg/L). The other 9 patients did not achieve normal plasma GH values. The latter patients subsequently received a 30 mg im SR lanreotide injection every 10 days. After 3 months of such a regimen, the plasma GH value in this subgroup decreased from 7.6 ± 0.9 to 5.7 ± 0.6

TABLE 1. Clinical characteristics of the 22 acromegalic patients before SR lanreotide treatment

Patient no.	Age (yr)	Sex	Tumoral status	Mixed adenoma	Surgery	Octreotide treatment		
						Dose (μg/day)	Mode[a]	Duration (months)
1	63	F	macro			300	inject × 3	6
2	52	F	micro			200	infusion	22
3	73	F	macro			600	infusion	27
4	44	F	micro	GH + PRL[b]	+	200	infusion	16
5	57	F	macro			600	infusion	6
6	62	M	macro			600	infusion	6
7	40	M	macro	GH + PRL[c]	+	500	infusion	34
8	59	F	macro			600	inject × 3	20
9	25	M	macro		+	300	inject × 3	6
10	52	M	micro		+	600	inject × 3	6
11	30	M	micro					
12	64	M	empty sella			300	inject × 3	6
13	47	M	macro		+	300	infusion	74
14	65	F	micro			600	inject × 3	7
15	64	F	macro	GH + PRL[d]		600	infusion	6
16	30	F	macro		+	300	inject × 3	8
17	54	F	micro		+	200	inject × 2	8
18	44	M	macro			100	inject × 2	24
19	49	M	micro			300	inject × 3	18
20	52	F	macro			300	inject × 3	12
21	54	F	micro			300	inject × 3	6
22	60	F	empty sella			300	inject × 3	12

[a] +, surgery completed. sc injection repeated twice or thrice a day according to the patient.
[b] Bromocriptine 7.5 mg.
[c] Bromocriptine 30 mg.
[d] CV 205 502 0.225 mg.

TABLE 2. Serum GH and IGF-I values during octreotide and long-term SR lanreotide treatment in acromegalic patients

Patient no.	GH (μg/L)					IGF-I (ng/mL)				
	Octreotide 6 months	Wash-out 7 days	SR lanreotide 3 months	SR lanreotide 1 yr	SR lanreotide 3 yr	Octreotide 6 months	Wash-out 7 days	SR lanreotide 3 months	SR lanreotide 1 yr	SR lanreotide 3 yr
1	1.07		5.98	5.37		309		498	788	
2	2.80	1.92	2.65	2.02	3.80	149	314	292	79	136
3	3.11	5.80	5.18	5.12	4.06	101	419	520	168	240
4	1.45	3.08	4.30	3.43	3.60	81	396	242	275	279
5	3.06	20.9	3.35	2.72		124	680	270	238	
6	0.90	12.2	6.58	3.11		163	750	497	204	
7	1.30	4.70	4.62	7.00	5.67	175	614	674	111	394
8	2.10	5.76	4.77	6.76	5.85	141	622		466	300
9	1.86	4.87	3.70	2.41		236	375	285	293	
10	4.80	5.80	10.4	10.3	6.21	310	470	267	445	767
11[a]			5.47	4.5				928	387	
12	0.72		2.23	7.60		133		312	455	
13	3.00	6.24	3.93	6.15	2.20	374	504	156	376	238
14	4.80		5.30	5.30	5.00	142			346	436
15	4.50	9.60	7.02	5.00	1.60	511	682	324	190	180
16	2.00	6.00	1.70	0.90		280	693	319	386	
17	1.70	6.00	2.40	3.00	4.20	160	409	302	172	183
18	0.50	6.40	2.60	1.60		102	215	75	90	107
19	3.00	43.0	8.90	8.50		302	711	302	169	
20	3.40	57.0	13.6	5.00	8.70	150	646	240	215	577
21	1.20	5.80	1.80	2.50	1.40	102	290		108	96
22	1.10	12.8	3.50	4.50		140	390	180	111	

[a] Patient included based on the GH response (<5 μg/L) after the acute 100 μg sc octreotide test.

μg/L. Among these 9 patients, 3 had plasma GH values in the normal range. At the 6 month visit, GH levels were 5 μg/L or less in 15 of 22 patients (68%) and 2.5 μg/L or less in 6 of 22 patients (27.2%). In this cohort of acromegalic patients treated with SR lanreotide, mean GH levels stayed in the upper part of the normal range (Fig. 1)) and were significantly reduced as compared with the pretreatment values ($P < 0.05$) during the 1–3 yr follow-up period. In these acromegalic patients, there was no evidence of tachyphylaxis.

Effects of SR lanreotide on IGF-I concentrations

In these acromegalic patients, the mean plasma IGF-I value at diagnosis was 647 ± 67 ng/mL; it was lowered to 199 ± 24 ng/mL during octreotide treatment (Table 2). Figure 2 shows the changes of IGF-I concentrations in these acromegalic patients treated with SR lanreotide for up to 3 yr. Seven days after octreotide withdrawal, the mean serum IGF-I value was 541 ± 43 ng/mL. After 3 months of treatment with SR lanreotide, the mean IGF-I levels significantly decreased to 351 ± 45 ng/mL ($P < 0.01$) as compared with the pretreatment values. After 6 months of SR lanreotide treatment, the mean serum IGF-I levels fell to 278 ± 41 ng/mL ($P < 0.01$) and remained suppressed throughout the long-term follow-up. At the 6-month visit, 14 patients (63.6%) had plasma IGF-I in the normal range, and this percentage remained fairly constant throughout the protocol study.

Effects of SR lanreotide on pituitary tumor size

Initially, 12 of 22 patients presented macroadenomas with the largest diameter greater than 10 mm. Eight patients had microadenomas, and 2 patients had an empty sella. Seven patients had undergone pituitary surgery, performed at least one yr before the present study. A significant decrease of the pituitary tumor volume was observed in 3 patients with macroadenomas. No decrease in tumor size was observed in patients with microadenomas or intrasellar tumor remnants.

Tolerance

Glucose homeostasis. Glycosylated hemoglobin levels (normal range 4–6%) remained stable throughout the long-term SR lanreotide treatment (Table 3). In four patients with diabetes mellitus, insulin or oral hypoglycemic dosages were unchanged as compared with those before SR lanreotide treatment.

Thyroid function. TSH (normal range, 0.5–4.5 mU/L) and free T_4 (normal range, 9–19.3 pmol/L) were evaluated before and during SR lanreotide treatment. All patients had normal free T_4 concentrations before treatment. Mean TSH and free T_4 concentrations remained in the normal range throughout the study (Table 3). In 5 patients, the dosage of levothyroxine (Levothyrox, Merck Clevenot Lab, France) prescribed for hypothyroidism or after thyroid surgery was unchanged during the protocol.

Side effects. Minor digestive problems (nausea, mild abdominal pain, softened stools) during 48 h after im injection were reported by 13 patients. Moderate discomfort at the injection site, lasting less than 24 h, was reported in four patients, and in one repetitive, local pain lasting three days after each injection was noted. During octreotide treatment, one patient presented asymptomatic gallstones by ultrasonography, and gallstones remained unchanged during the SR lanreotide treatment. In 4 other patients (18%), gallstone formation was observed during SR lanreotide treatment. Three patients remained asymptomatic, but one underwent an elective cholecystectomy after an episode of acute cholecystitis.

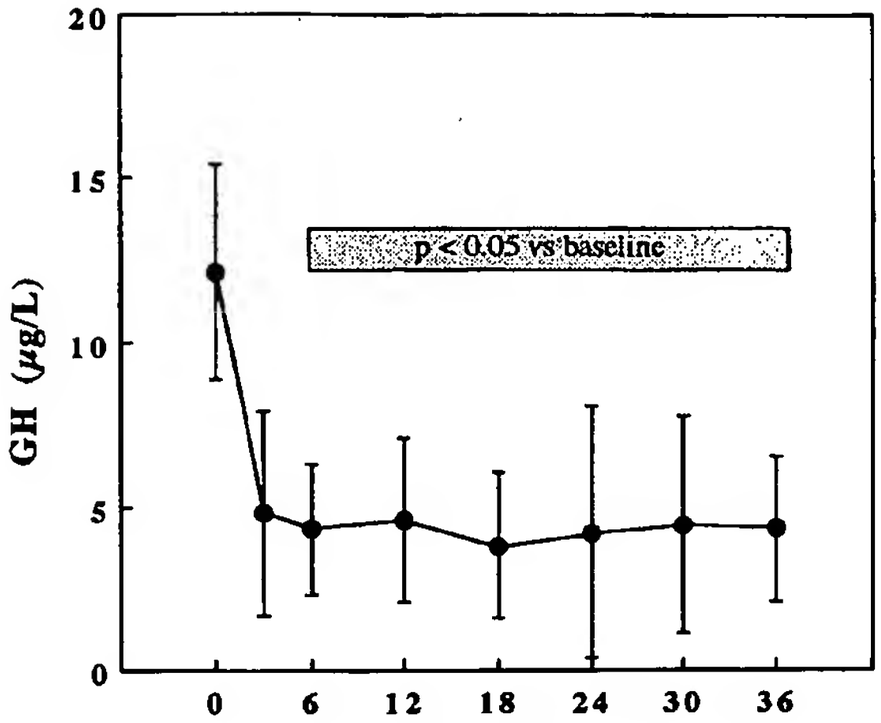

FIG. 1. Mean plasma GH concentrations (± SEM) in 22 acromegalic patients before and during long-term treatment with SR lanreotide.

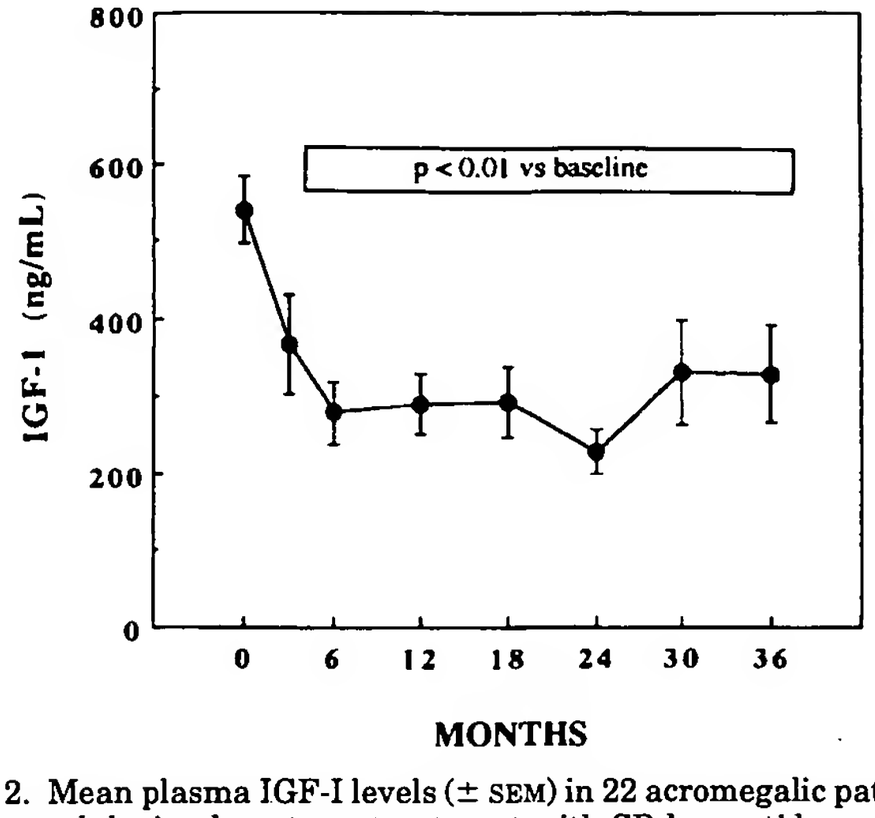

FIG. 2. Mean plasma IGF-I levels (± SEM) in 22 acromegalic patients before and during long-term treatment with SR lanreotide.

Discussion

This study demonstrates the efficacy and the safety of long-term SR lanreotide in the treatment of acromegaly for up to 3 yrs. Previous prospective studies with SR lanreotide treatment during a 6-month period have reported control of GH hypersecretion similar to that of octreotide therapy (6–8). In the present investigation, both GH and IGF-I concentrations remained significantly lower than pretreatment values for a period of up to 36 months.

The long-term effectiveness of somatostatin analogs on GH hypersecretion has been reported to be correlated with the number, distribution, and activity of somatostatin receptors on GH adenoma cells (11–13), as well as with the plasma concentrations of somatostatin analogs (3). After im administration of 30-mg SR lanreotide, plasma lanreotide levels reach the peak 2 h after injection because of the rapid release of the analog localized at the surface of the copolymer, then they decline during 48 h. Subsequently, they increase and then progressively decrease until day 10–14 following the injection (5, 14). Conversely, using a depot formulation of octreotide (Sandostatin-LAR), the plasma octreotide levels showed also a 2-phase pattern after im injection of 10–30 mg. Octreotide levels peak at 2 h and then decrease to low levels during the following 10 h. They remain low for 7 days and then start to increase, remaining elevated for 3–4 weeks (15). At the start of SR lanreotide treatment, the absence of this period with low concentrations of analog may explain the immediate efficacy of lanreotide on GH hypersecretion (6, 8) as well as the noticeable frequency of digestive problems reported during the first days after the im SR lanreotide injection.

On the basis of previous studies (4, 8), the acromegalic patients received 30 mg SR lanreotide twice monthly until the 3-month visit. Among the 22 patients, 13 presented with control of GH hypersecretion, whereas the other 9 patients did not achieve normal GH levels. These latter patients subsequently received a 30 mg SR lanreotide im injection every 10 days. After 3 months of such a regimen, 3 patients of this subgroup had mean plasma GH values in the normal range,

TABLE 3. Effects of long-term SR lanreotide treatment on glycosylated hemoglobin levels and thyroid function parameters

	Glycosylated hemoglobin (%)	TSH (mU/L)	Free T_4 (pmol/L)
Baseline	6.5 ± 0.5	1.44 ± 0.31	14.3 ± 0.6
6 months	6.8 ± 0.6	1.09 ± 0.21	15.4 ± 0.8
12 months	6.8 ± 0.5	1.48 ± 0.39	14.4 ± 0.8
18 months	7.2 ± 0.7	1.50 ± 0.31	15.4 ± 0.6
24 months	6.5 ± 0.5	1.38 ± 0.30	15.7 ± 0.9
30 months	6.0 ± 0.3	1.25 ± 0.46	15.8 ± 1.8
36 months	7.0 ± 0.8	1.08 ± 0.24	16.3 ± 1.4
Normal range	4–6	0.5–4.5	9–19.3

and the other 6 patients did not normalize GH concentration with SR lanreotide treatment. The reduction in GH values and the long-term control of GH hypersecretion with the change in the SR lanreotide regimen might be the result of a possible cumulative effect of repeated injections, as previously shown in acromegalic patients treated with either octreotide (16) or SR lanreotide (4). Therefore, the results of this study suggest that a GH evaluation after a 3-month period with 2 monthly injections may indicate the frequency of SR lanreotide im injections needed to maintain an efficient control of plasma GH concentrations. However, a definite conclusion requires the study of more acromegalic patients treated with SR lanreotide.

In this group of 22 acromegalic patients, the mean GH values decreased during SR lanreotide treatment, but remained in the upper part of the normal range during the 1–3 yr follow-up period. No escape from the SR lanreotide treatment occured. These results are comparable to those observed during long-term treatment with octreotide (13, 17). On the other hand, 2 long-term studies have shown that normalization of GH levels is one of the best determinants of therapeutic outcome in acromegaly (18, 19). Among our acromegalic patients, 27.2% had suppressed GH secretion to less than 2.5 μg/L. However, these results might be related to the fact that GH evaluation (just before the next SR lanreotide im injection) was probably made at the time of the lowest circulating level of somatuline (4).

During long-term treatment with SR lanreotide, IGF-I concentrations were lower than those observed before somatostatin analog treatment. In 14 of the 22 patients (63.6%), im injections of SR lanreotide allowed normalization of IGF-I levels after 6 months of treatment, and the result remained unchanged during the 3-yr follow-up period. These results are similar to those reported during octreotide therapy (20). Therefore, during SR lanreotide treatment, serum IGF-I decreased more markedly than GH levels. A similar dissociation has been reported during treatment with octreotide (21). The difference between GH and IGF-I responses during SR lanreotide treatment may be that GH measurements were made at the time of hormone release but not when the beneficial effect of SR lanreotide on overall GH secretion occured (4). Therefore, during SR lanreotide treatment, serum IGF-I values appeared to be a better marker of drug efficacy and possibly a better predictor of long-term effect than serum GH concentrations.

A reduction of tumor size has been reported in approximately half of acromegalic patients treated with octreotide (22–24). In this series, a significant decrease of the pituitary tumor volume was observed in 3 patients, as assessed by computed tomography scan or magnetic resonance imaging. The relative effect of SR lanreotide on pituitary tumor size may be related to the fact that the majority of patients included in this study had been previously operated and/or treated for a long period with octreotide.

SR lanreotide appeared to be well-tolerated throughout the study, and the patients continued im injections of SR lanreotide after the end of the 3-yr study. The main side effects consisted of minor digestive problems (nausea, mild abdominal pain, softened stools) during 48 h after each injection and were reported by 13 patients. Gastrointestinal side effects observed in our patients are comparable to that reported in previous studies (4, 6–8). During SR lanreotide treatment, there was no evidence of a significant alteration in glucose tolerance and thyroid function: mean glycosylated hemoglobin levels and mean free T_4 concentrations remained in the normal range (2, 25). The most potentially important side effect of long term administration of somatostatin analogs is an increased tendency to gallstone formation. In our patients, biannual gallbladder echographies revealed the occurence of gallstones in 4 patients (19%). The incidence of gallstone formation during long-term octreotide therapy administered as two or three injections ranges from 20–50% (26, 27), whereas it is 18.5% during continuous sc infusion (28). Tauber *et al.*(28) suggested that continuous somatostatin analog therapy might up-regulate the sensitivity of the gallbladder to cholecystokinin and thereby, at least partly, restore gallbladder contraction.

In conclusion, this 1–3 yr follow-up study confirms the efficacy and the safety of the SR lanreotide administration in acromegaly. Therefore, after unsuccessful surgical and radiotherapeutic treatment, SR lanreotide appears to be a useful therapeutic tool in acromegalic patients that will need long-term somatostatin analog therapy.

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